Remarks

Prior to entry of this amendment, claims 80, 81 and 90-97 were pending; of these, claims 91-93 are withdrawn from consideration. By this amendment, claims 90 and 94-97 are amended; and new claims 100-103 are added. Applicants reserve the right to pursue at a later date any subject matter removed from consideration by this amendment.

Support for the amendments and newly added claims can be found throughout the specification. Exemplary support for the amendment of claim 90 to recite an "aberrant" activity can be found in in the specification at page 23, lines 23-27. Exemplary support for the amendment of claims 94-97 to recite "angiogenesis-mediated growth of a solid tumor" can be found in the specification at page 27, lines 1-7 and lines 8-16. It is well-recognized that tumors that develop from the neoplasms listed in the specification and recited in the claims (*i.e.*, sarcoma, carcinoma, lymphoma, malignant melanoma, or benign tumors) will develop as "solid" tumors. Exemplary support for new claims 100-103 can be found in in the specification at least at page 27, lines 1-7 and lines 8-16.

No new matter is introduced by the amendments made herein, including the newly-added claims. After entry of this amendment, **claims 80, 81, 90-97, and 100-103 are pending in this application** (of which claims 91-93 are withdrawn).

Information Disclosure Statement

Applicants thank Examiner Pagonakis for acknowledging that she considered the references cited on the Information Disclosure Statement submitted to the Office on September 10, 2010.

Applicants note that the Examiner did not indicate that U.S. Patent No. 6,080,750 was considered. Applicants respectfully request that the Examiner acknowledge that this reference was considered in a subsequent action. For the Examiner's convenience, a copy of the partially-signed Form 1449 is provided herewith.

Restriction/Election

Applicants note that the Office has withdrawn claims 91-93 as directed to non-elected subject matter. Applicants note that claims 92 and 93 are newly withdrawn in the current action. These claims were substantively examined in the Non-final Office action dated February 22, 2010 and the Final Office action dated June 10, 2010. In the interests of compact prosecution, Applicants respectfully request that these claims be recombined and examined.

Applicants additionally request rejoinder and examination of claims 91-93 upon allowance of generic claim 90.

Withdrawn Rejections

Applicants thank Examiner Pagonakis for acknowledging that previous arguments were successful in overcoming the enablement rejection under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §102(b)

Claims 80, 81, 90 and 94-97 are rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Japanese Patent No. 10212235 (hereafter JP10212235). The Office asserts that JP10212235 describes "a compound of formula (I) wherein the compound is that of instant claim 80 . . . . [and] it is taught that the compound of formula (I) is effective for the treatment of tumors" (Office action, at page 3). The Office further asserts that "though JP 10212235 is silent as to the effect of the elected compound to inhibit an activity of gastrin releasing peptide (GRP), the administration of the claimed compound to patients suffering from cellular proliferative disorders is expected to necessarily have the claimed effect of inhibiting an activity of GRP, whether recognized by the author or not" (*Id.*). Applicants traverse this rejection for the following reasons:

JP10212235 does not describe inhibition of angiogenesis or angiogenesis-mediated growth of a solid tumor

The MPEP at §2131 states that "to anticipate a claim, [a] reference must teach every element of the claim." The Office has limited examination to methods of treatment of a "cellular proliferative" condition and asserts that the pending claims are anticipated by JP10212235. In

contrast to this assertion, Applicants note that instant claim 94 depends from claim 92, which recites that the condition being treated is "mediated by aberrant angiogenesis." When read with the limitations of claim 92, claim 94 thus requires that the recited condition be a cellular proliferative condition that is "mediated by aberrant angiogenesis." To clarify this distinction, and only in order to advance prosecution in this application, claim 94 has been amended to recite that the cellular proliferative condition is "angiogenesis-mediated growth of a solid tumor." Applicants submit that JP10212235 neither expressly nor inherently describes use of any compound and certainly not Applicants' claimed compound to treat "angiogenesis-mediated growth of a solid tumor."

JP10212235 describes generic compound I (hereafter Compound I) and 131 species thereof for use as agents to treat "various kinds of tumors" (JP10212235, ¶1). In contrast to the subject specification, JP10212235 does not describe the effect of any compound on angiogenesis. In particular, JP10212235 does not describe the use of any of the described compounds to treat angiogenesis-mediated growth of a solid tumor. Indeed, Applicants note that the word "angiogenesis" does not seem to appear in the machine translation of JP10212235 at all. Moreover, none of the data presented in JP10212235, either expressly or implicitly, demonstrates inhibition of angiogenesis or angiogenesis-mediated growth of a solid tumor. The cellular proliferation assays presented in Tables 27-31 are also described at paragraph 70 as showing "antitumor action," but these experiments only show growth inhibition of cultured cell lines and not inhibition of solid tumor growth. Additionally, the sole *in vivo* study measures the survival of mice injected with a leukemia cell line, which does not form angiogenesis-dependent solid tumors. Thus, JP10212235 provides no teaching that would indicate to one of skill in the art that the asserted anti-proliferative effect of Compound I or its species is in any way related to inhibition of angiogenesis-mediated tumor growth.

JP10212235 does not inherently describe inhibiting an aberrant activity of GRP with Compound 77427

The MPEP at §2112 describes the "Requirements for Rejections Based on Inherency." In describing the rationale or evidence necessary to establish inherency, the MPEP states that "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient

to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)" (citations omitted). Applicants submit that the description in JP10212235 is not sufficient to establish inherent anticipation of Applicants' claims under the requirements set forth by the MPEP.

JP10212235 identifies generic compound I and 131 species thereof as potentially having antitumor properties. The Office asserts that one such species, Compound 105, is identical to Applicants' compound of formula XV' (hereafter Compound 77427), which is recited in Applicants' pending claims. JP10212235 describes *in vitro* tests of anti-cellular proliferative activity using nine of the 131 species on 54 cancer cell lines, and a single *in vivo* test using one such described species. JP10212235 does not describe the effects of any compound on GRP activity, nor is GRP mentioned at all. Additionally, and without admission to any similarity between Compound 105 and claimed Compound 77427, Applicants note that Compound 105 is not among the compounds used in the *in vitro* tests of anti-cellular proliferative activity, and Compound 105 is not used in the single *in vivo* study.

Moreover, as discussed below, from the data presented in JP10212235, it would not be possible for one of skill to envisage <u>any</u> commonly-shared and "necessarily present" property of generic Compound I and all 131 described species. Applicants submit that if an antitumor property of Compound 105 cannot be envisaged from JP10212235, it would be impossible for this reference to inherently anticipate the effect of this compound on aberrant GRP activity.

JP10212235 asserts that generic Compound I and its species possess antitumor properties based on two sets of experiments. The first set of experiments (shown in Tables 27-31) presents

the *in vitro* effect of nine species (Compound 14, 44, 45, 63, 64, 70, 71, 78, or 125) on proliferation of 54 different cancer cell lines. Notwithstanding any inhibitory effect on cellular proliferation demonstrated by these compounds, the data presented in Tables 27-31 does not show an anti-proliferative effect of **every compound** against **every cell line** tested. In each of the tables, at least one of the tested compounds has no indicated anti-proliferative effect on at least one of the tested cell lines. Indeed, the omissions in some of the tables (*see* for example Table 30, Compounds 44, 45, and 63) demonstrate **considerable variability** among the biological effects of the tested compounds. The second set of experiments (presented in Table 32) involves administration of Compound 44 to mice that were injected with a leukemia cell line, and measurement of subsequent survival time. No measurement of *in vivo* effect on proliferation was made (nor was the leukemia cell line among those used in the *in vitro* assays), and no other compound was tested for *in vivo* effect. Thus, not only is the data presented highly variable, but the only *in vivo* experiment described involves use of a single compound and does not measure *in vivo* antitumor activity.

Applicants note that there are distinct structural differences between the compounds used in the experiments described in JP10212235 and Compound 105. As presented in **Exhibit A**, it is clear that all of the compounds used in the *in vitro* and *in vivo* experiments have a cyclic, branched functional group at position R3 that is distinctly different from the non-cyclic, unbranched R3 group of Compound 105. Because of these structural differences, one of skill in the art could not necessarily infer a biological property of Compound 105 from a property possessed by the other compounds presented in **Exhibit A**.

Taken together, Applicants submit that the data presented in JP10212235 would not allow one of skill in the art to infer any general biological effect common to generic Compound I and all 131 species mentioned. Moreover, the structural differences between Compound 105 and the compounds actually tested in JP10212235 also would not allow any inference of commonly-shared antitumor properties. Because no such inferences can be made and because JP10212235 does not otherwise establish an antitumor effect of Compound 105, one of skill in the art could not envisage such a property of Compound 105. By extension, the ability for Compound 105 to inhibit an aberrant GRP activity cannot be "necessarily present" in JP10212235. Thus,

JP10212235 does not inherently anticipate a method of treating a condition by inhibiting an aberrant GRP activity with Compound 77427.

For the foregoing reasons, JP10212235 does not anticipate claims 80, 81, 90 and 94-97 (or withdrawn claims 91-93). Applicants request withdrawal of this rejection under 35 U.S.C. §102(b).

JP10212235 does not anticipate new claims 100-103

New claims 100-103 recite methods of "inhibiting angiogenesis-mediated growth of a solid tumor." As discussed above, JP10212235 does not describe inhibition of angiogenesis-mediated growth of a solid tumor. Accordingly, Applicants submit that new claims 100-103 are not anticipated.

Rejoinder of Withdrawn Claims

Applicants note above that withdrawn claims 92 and 93 were examined in prior actions, and accordingly request their rejoinder. Moreover, Applicants submit that based on the foregoing arguments, generic claims 80 and 90 are in condition for allowance. Applicants request that claims 91-93 be rejoined, examined, and allowed at this time.

Conclusion

Based on the foregoing amendments and arguments, the pending claims are in condition for allowance, and notification to that effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of the claims, please telephone the undersigned at the telephone number listed below.

Respectfully submitted,

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